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Review

Burn resuscitation

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ABSTRACT

Current guidelines outlining the resuscitation of severely burned patients, in the United States, were developed over 30 years ago. Unfortunately, clinical burn resuscitation has not advanced significantly since that time despite ongoing research efforts. Many formulas exist and have been developed with the intention of providing appropriate, more precise fluid resuscitation with decreased morbidity as compared to the current standards, such as the Parkland and modified Brooke formulas. The aim of this review was to outline the evolution of burn resuscitation, while closely analyzing current worldwide guidelines, adjuncts to resuscitation, as well as addressing future goals.

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1. Introduction

Resuscitation after severe burn, specifically in the first 24 h after injury, has been and remains a taxing assignment for all burn care providers, regardless of level of training. Accepted guidelines (Parkland and modified Brooke formulas) provide a foundation for focused resuscitation boundaries, and remain the mainstay of what is taught about initial resuscitation around the world, from first responders to intensivists and trauma surgeons. The large difference in recommended total fluid between these accepted formulas of resuscitation, exemplifies the ongoing controversies that exist in applying appropriate therapy [1–3]. Many studies exist that examine alterations or adjustments in resuscitation protocols that may

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lead to improved outcomes, however, none are definitive nor have replaced the tried and true standards. The fact remains that these guidelines, even if followed closely, do not always insure a smooth resuscitation, and under-resuscitation and over-resuscitation after severe burn and associated morbidity continue to plague providers and patients despite any advances in therapy [4–8]. This can be related, to some extent, to the difficulty in implementing the Parkland or Brooke formulas during signs of physiologic decompensation such as hypotension or systemic acidosis. Often, this leads to high infusion rates in an attempt to augment cardiac preload that may or may not be effective, or in fact may be harmful. Also, this notion leads to a high rate of non-compliance with these formulas by many inexperienced providers.

Many very important advances in burn resuscitation were made over the last 60 years, although very little of significance has developed since the 1960s and 1970s when Baxter and Pruitt focused research efforts in burn resuscitation and proposed the Parkland and modified Brooke formulas, respectively [9]. Many questions remain unanswered and future considerations are plentiful in this difficult arena. The goal of this article is to review burn resuscitation evolution, understand how we have arrived at today's guidelines, and reiterate the questions that continue to befuddle and should be addressed in future studies.

2. History

Burn resuscitation studies date back to the early 20th century with Haldor Sneve's description of burn treatments in the Journal of the American Medical Association (JAMA) in 1905 [10]. Sneve proposed methods of preventing shock after severe burn by the administration of salt solutions to severely burned patients by various modalities. These included solution administration through oral ingestion, clysis, enemas, and intravenous infusion. He also described many important concepts regarding skin grafting and metabolic wasting of burn patients in addition to his observation of fluid requirements in the patient with severe burns. Sneve wrote, ''In areas involving large areas of skin the patient is exposed to death first from shock ...'' [10]. In describing the pathophysiology leading to the shock state seen in burns he postulated that various irritants, mental and physical, caused vasomotor paresis leading to accumulation of blood in the splanchnic vessels depriving the peripheral vasculature of adequate fluid volume. In treating shock, Sneve recommended to first treat the vasomotor paresis with adrenalin only. Second, to drive accumulated abdominal blood back into the periphery by using enemas and drinks composed of normal saline solutions. Also, he added that more fluid should be administered using saline solution transfusions or clysis into the skin to give the heart something to work on [10]. However, his recommendations were not largely accepted or followed for many more years [11].

Years later, an unfortunate coal dust explosion producing severe burns in 32 people led to a publication from Fauntleroy describing their care. In 1919, he described the various techniques employed in resuscitation of these extensively burned patients, who received a regimen of normal salt solution with added sodium bicarbonate through proctoclysis. Oral fluid administration ensued after initial proctoclysis that consisted of water and liquid nutritional supplements, described as ''eggnogs'', every 2 h to which whiskey, i.e. corn distillate with a high ethanol content, was added during the night. Fauntleroy, in addressing the wasting seen in severe burn patients weeks after injury, goes on to describe a tonic comprised of quinine, strychnine, and phosphorus that was used to treat this state of 'exhaustion' [12]. This protocol of treatment, although unorthodox especially by today's standards, exemplifies the lack of significant advancement in burn resuscitation seen in the early decades of the 20th century.

In 1921, Underhill described his studies of patients burned in the Rialto Theatre fire in New Haven [13]. Underhill expressed how systemic shock seen in his severely burned patients was related to initial fluid losses not immediately obvious to casual observers. The important concept described by Underhill was the understanding that the fluid accumulating in edematous tissue after burn was actually filtrate of circulating plasma. Prior to this, little documentation specifically dealing with burn resuscitation was extant.

Alfred Blalock, in a 1931 publication, commented upon hemodynamic parameter alterations, specifically in blood pressure, and its relation to the edema found in burned tissue [14]. He studied mongrel dogs that were burned on one side of the body and then compared the weights of the burned tissue to the tissue on the unburned side. Serial incisions in the burned tissue demonstrated the progressive increase in tissue edema over time. This increase in edema observed was also correlated with blood pressure measurements at the same intervals. He concluded that the decrease in blood pressure noted was related to the degree of edema found in the burned tissue. His findings supported those of Underhill suggesting that burned tissue edema was essentially a filtrate of plasma (Fig. 1).

One of the first specific recommendations regarding burn resuscitation that attempted to use particular clinical indices to direct fluid therapy was initiated at the beginning of World War II. Hematologic laboratory values of peripheral blood, i.e. hematocrit and hemoglobin concentration, were used to identify degree of hemoconcentration at various time points after severe burn during resuscitation; fluid therapy dosing

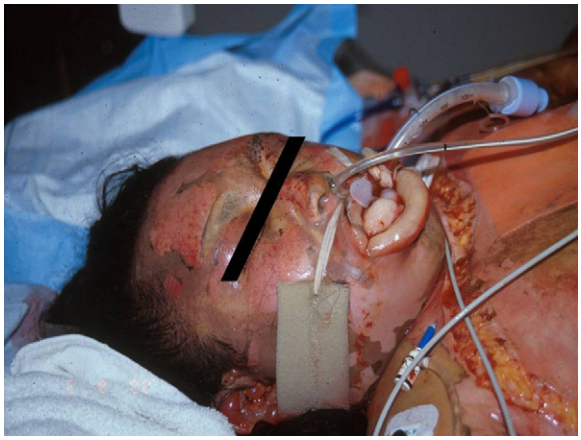

Fig. 1 – Profound edema seen in severe burns during resuscitation.

recommendations were then based on degree of hemoconcentration [15–17]. This therapy fell out of favour with recognition that these recommendations failed to account for ongoing losses that occur after identifying the degree of hemoconcentration, essentially a snapshot in time. In essence, patients treated in this manner were under-resuscitated and it was acknowledged that a more standardized formula of resuscitation was warranted to improve patient outcomes.

January 1942 was a pivotal time in burn history as the National Research Council, under Chairman Isadore S. Ravdin, agreed that a new standardized approach to burn resuscitation based on surface area of burn should be recommended to the military. Dr. H. Harkins accepted the challenge, and using his observations from studies in canine burn models, proposed the first well-known burn resuscitation formula based on extent of *surface area burned* as a key guide dictating fluid therapy. His proposal stated that all patients with greater than or equal to 10% body surface area burn should be resuscitated with 1000 cm^3 of plasma for each 10% surface area burned, to be administered over the first 24 h after injury [17]. Interestingly, at that conference, the Board recommended the use of a crystalloid solution (5% dextrose in physiologic saline solution) administered at a rate of 20–40 drops per minute, in addition to the plasma, but only after sufficient plasma had been given to restore proper circulating volume [18] (Table 1).

Cope and Moore published their experience with burns related to the Coconut Grove Disaster of 1942, where they suggested a relationship between systemic shock after burn and generalized edema development. This paper, considered a landmark publication by many, was recognized as the first to suggest that resuscitation should be formulated from the patient's body weight *and* extent of burn [19]. They acknowledged the shortcomings of a formula based on surface area burned alone, and described their findings related to interstitial space expansion and its important relationship to renal function and/or failure. Cope and Moore also emphasized the concept of increased fluid needs of patients with pulmonary injury due to smoke. They proposed a resuscitation formula called the 'Body-Weight Burn Budget,' using colloid and electrolyte solutions, based on anticipated interstitial space expansion according to body weight given over the first 48 h after burn. Evans followed years later with the 'Evan's formula' that was the first to calculate fluid requirements based on body weight and total body surface area (TBSA) burn [20]. This formula, which included colloid consisting of albumin instead of plasma because plasma fell out of favour for risk of bloodborne disease transmission. This formula was the basis of fluid resuscitation for many years.

C.P. Artz from the Army Burn Center in San Antonio followed with a modified version of Evan's formula which placed more emphasis on crystalloid resuscitation and a decreased dose of colloid for burn resuscitation, especially in the first 24 h after injury. The basis for this difference lies in Dr. Artz's description of the changes in plasma composition immediately after severe burn. He states that water and electrolytes were lost into the burn wound at a greater rate than protein losses. Artz referred to the earlier work of Fox describing the dramatic sodium shifts into the cells and interstitium seen in burns, leading to an intravascular hypo-osmolar state. Addressing the replacement of sodium losses due to electrolyte shifts through the use of more crystalloid and less colloid within the first 24 h after severe burn became the key factor in Dr. Artz's proposed resuscitation guidelines. This formula came to be known as the Brooke formula [21]. These formulas were the basis for burn resuscitation for years until further controversy arose over the role of colloids in burn resuscitation formulas.

Moyer and others, in 1965, described their studies of burn shock in relation to extravascular sodium concentrations [22]. Their general focus was on the distribution of sodium and other oncolytes during resuscitation. This led to the development of formulas composed only of crystalloid. This change in approach set the stage for a boom in research in this area with focus placed on burn resuscitation strategy. In the late 1960s through the 1970s, investigators at the Institute of Surgical Research (ISR) in San Antonio and at Parkland Hospital in Dallas emerged as the dominant figures in burn resuscitation research from which the widely accepted Parkland formula was proposed [23]. Pruitt et al. from the ISR promptly followed with a recommendation calculating fluid requirements as in

Table 1 – Historical overview of various burn resuscitation formulas

1942	Harkins formula	Any patient with at least a 10% burn: administer 1000 cm^3 plasma for each 10% total surface area burn over first 24 h
1947	Body-Weight Burn Budget	First 24 h: 1–4 LLR + 1200 ml 0.5 NS + 7.5% body weight colloid + 1.5–5 l D_5W. For second 24 h: same formulation except change colloid to 2.5% body weight
1952	Evan's formula	First 24 h: NS at 1 ml/kg/% burn + colloids at 1 ml/kg/% burn + plus 2000 ml glucose in water. Second 24 h: one-half the first 24 h crystalloid and colloid req. + the same amount of glucose in water as in the first 24 h
1953	Brooke formula	First 24 h: LR at 1.5 ml/kg/% TBSA burn + colloid at 0.5 ml/kg/% TBSA burn. Second 24 h: switch to D5W 2000 ml
1974	Formula	First 24 h: LR at 4 ml/kg/% TBSA; give half in first 8 h and the remaining over next 16 h. Second 24 h: colloid at 20–60% of calculated plasma volume to maintain adequate urinary output
1979	Modified Brooke	First 24 h: LR at 2 ml/kg/% TBSA burn, one half in the first 8 h and half in the remaining 16 h. Second 24 h: colloid at 0.3–0.5 ml/kg/% TBSA burn + D5W to maintain urine output
1984	Monafo formula	First 24 h: saline with 250 mequiv. Na + 150 mequiv. lactate + 100 mequiv. Cl. Rate adjusted per urine output. Second 24 h: one third of isotonic salt administered orally

the Brooke formula without the use of colloids in the first 24 h of resuscitation [24]. This became known as the modified Brooke formula.

In 1970, Monafo presented his experience with the use of hypertonic saline as the principal solution for initial burn resuscitation [25]. The basis for this treatment lay in the notion that hypertonic saline returns water from the cells and interstitium to the intravascular space, necessitating decreased edema and decreased resuscitation volumes. Subsequent studies suggested a decrease in abdominal compartment syndrome (ACS). Oda et al., in 2006, published their experience with hypertonic saline vs. lactated Ringer's [26]. The primary endpoint evaluated was abdominal compartment syndrome which they defined as intra-abdominal hypertension (intra-abdominal pressure > 30 cm H_2O measured by bladder pressure) in association with a clinically tense abdomen, combined with high peak inspiratory pressures (PIPs) that compromised appropriate ventilation or oliguria despite aggressive fluid resuscitation. To decrease elevated intra-abdominal pressures, nasogastric tube decompression as well as pharmacologic paralysis was initiated. Patients were randomly assigned to the hypertonic lactated saline (HLS) group or the LR group. No significant differences were noted in burn size, severity, or other demographic data. They reported a significant decrease in required fluid loading to maintain adequate urine output (UOP) in the HLS group as compared to the LR group. As well, peak inspiratory pressures were noted to be significantly less at 24 h after injury in the HLS group. Fourteen percent of the patients in the HLS arm compared to 50% in the LR arm developed IAH at approximately 24 h after burn. Based on these observations, the authors suggested that the use of HLS in initial fluid resuscitation management of severe burns could decrease the incidence of ACS [26]. However, others have proposed an increase in renal failure as a cause for concern [27] (Fig. 2).

Many new formulas and derivations of old guidelines have been proposed since the surge in the mid-century with little success in altering the current practice of adhering to the Parkland formula [28–32]. As is evidenced by the multiple proposed formulas over the last century, it should be clear that the complex nature of burn pathophysiology, particularly in severe burns and its therapy, impedes any quick and easy solution to this taxing dilemma. As is true in many arenas, and is no different in systemic shock related to acute burn, it is necessary to understand the history of a problem to understand how we have arrived at today's solutions and consequent contemporary problems in order to design novel approaches to address these problems while maintaining current standards for outcomes.

We have examined the history of burn resuscitation briefly. In the following paragraphs, we will more closely evaluate the formulas that are the present mainstay of resuscitation guidelines for severe burns around the world.

3. The Parkland formula

The development of the Parkland formula in 1968, a crystalloid only formula by Baxter and Shires, stemmed from elucidation of important concepts in burn physiology from their studies

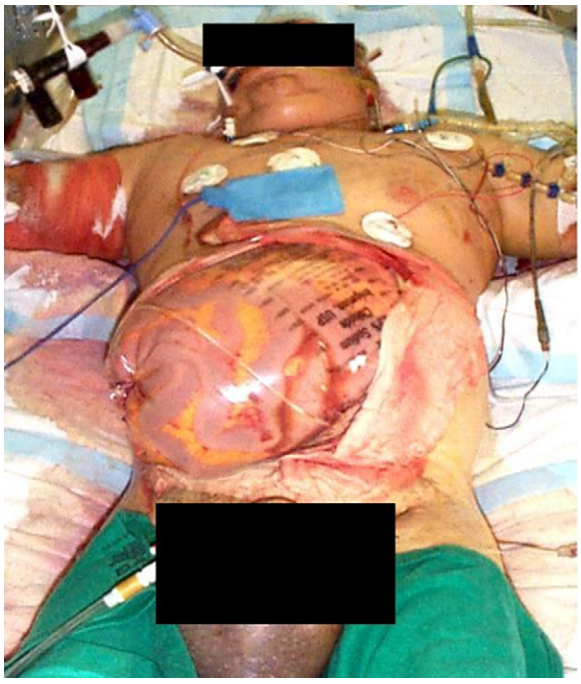

Fig. 2 – Abdominal compartment syndrome in severe burns is associated with a 70–100% mortality rate.

on fluid shifts between compartments seen after severe burn [33]. Although these data originated the most widely used burn resuscitation formula today, issues arise after careful review of the landmark article proposing the Parkland formula. The publication describes several elegant experiments, beginning with a description of the natural history of fluid shifts in response to severe burn (40% TBSA) without resuscitation in rhesus monkeys. These animals were untreated for the injury with only measurement of red cell mass, plasma volume, electrolyte movement, and extracellular fluid to assess the natural history of fluid and electrolyte shifts after burn. Similar measurements were made of edema fluid collected by aspiration from multiple incisions made in the wounds. They showed that edema fluid was no different from plasma in sodium or potassium concentrations, and that red cell volume fell approximately 10%, plasma volume fell 25%, and extracellular fluid volume fell 40%. However, we are not given data regarding the variability of the measurements which brings further questions in this regard.

Further experiments of 30% TBSA flame burns in mongrel dogs without spleens were made on which to formally conduct resuscitation experiments. They found the nadir in decreased cardiac output at 4 h after injury to approximately 30% of control values which corresponded to a 25% decrease in extracellular fluid and a 20% decrease in plasma volume. At 18 h, cardiac output had corrected significantly, while plasma volume continued to fall by 26% and extracellular fluid by 30%. Therefore, cardiac output improved in spite of continued losses of volume suggesting loss of contractility that began to recover as well as lower volume loading.

Then, they used dogs with a 50% TBSA burn to measure cardiac output and arterial blood gases and lactate before and at intervals after burn. These animals, as opposed to the other

experiments, were treated with lactated Ringers' solution beginning 1 h after injury. They performed several series of these experiments (12 dogs/group) with varying resuscitation volumes. They found that the optimal cardiac output response in animals treated with 16–20% of the beginning weight given in the first 8 h that was maintained with an additional 8–10% of weight given in the next 16 h. A criticism is that we are told that this was the best regimen rather than shown the data for comparison, in particular the 8 h division is not justified. In fact, it appears that at 24 h, extracellular volume is approximately 25% higher than control using this regimen, thus potentially increasing rigid or semi-rigid compartment pressures such as the abdomen or anterior compartment of the leg. Regression of changes in volume infused to changes in cardiac output in the first 8 h and thereafter would offer more introspection of the data.

In the last part of this study, they showed that their derived formula was reasonable for resuscitation in humans with burns between 30 and 85% TBSA. One glaring problem with the data as presented is we are given the crystalloid intake in % of body weight without the actual weights used, so further derivations by the reader are not possible. Again, no mention of any background data that supports the protocol of dividing the weight based calculated fluid dose into an 8-h interval and a 16-h interval is given. We now wonder why this is the standard.

In the final experiments in human subjects, fluid was administered at a rate of 3.5–4.5 cm^3 LR/%TBSA/kg body weight over 24 h. No definite formula derivation is presented that describes exactly how they arrived at this dose, although we suppose that it was inferred from the animal data with adjustment for human weights. An area of difference from today's standard relates to monitoring of urine output. Baxter described that this formula was used until a urine output of 50 cm^3/h was achieved and then the rate of LR administration was decreased to maintain this volume of output. Current accepted standards allow for a urine output goal of approximately 30 cm^3/h in an average adult which itself arises from the notion that this is the minimal hourly amount of urine required for solute disposal in normal unburned people. Therefore the question arises whether this formula was derived from goals that essentially seek to over-resuscitate. Second, the goal in the pre-clinical development of the Parkland formula was to maintain cardiac output, not urine output. However, this is the standard practiced worldwide today because of the notion that urine output is a proxy for cardiac output, but is this true? [33]. In other words, is the urine output a.k.a. cardiac output attained by attending to this formula necessary and therefore beneficial, or is it in fact harmful? We cannot know unless it is tested against other standards. We understand that these will be difficult experiments to undertake for ethical reasons unless the endpoints measured are different.

Nonetheless, a very important finding in Baxter's and Shires' study is that fluid losses were occurring at a faster rate that previously described. That concept alone is at the core of resuscitation research still today, and many studies are currently designed to fine tune the optimal resuscitation for burned patients. Another very important area addressed by Baxter supports that of a potential myocardial depressant factor thought by others to be present in large burns [34]. Initially, animal subjects were seen to exhibit a progressive decrease in cardiac output after burn to the extent where the majority of the animals expired between 48 and 96 h despite aggressive fluid, inotropic, and vasoactive drug support. The decrease in cardiac output was related to decreases in preload as demonstrated above, but the decreases are more than would be expected from decreased preload alone suggesting a direct myocardial depression of severe cutaneous burn. Their animal data also suggest that this independent myocardial depression begins to improve at 4–8 h, perhaps justifying the recommended change in fluid volume rate after 8 h in their final formula, but this is not clearly enumerated. Baxter claims to demonstrate the probable existence of this factor in humans as well. Sera from a number of human subjects in this study, exhibiting failure to sustain normal cardiac output after burn, were shown to demonstrate a negative inotropic effect on *in vitro* heart preparations [34].

The Parkland formula remains the most widely used resuscitation formula in the world, although only the initial 24 h crystalloid portion of the formula is the portion followed closely, with little attention focused on the colloid recommendations presented for the second 24 h after burn. Although a very important publication in the history of burn treatment, these guidelines developed by Baxter et al. were proposed over 30 years ago. Many important questions and concerns arise when critically reviewing this paper and applying today's standards of sound experimental design and reporting.

4. The modified Brooke formula

The original Brooke formula proposed by Dr. Artz at the Army Burn Center was composed of both crystalloid and colloid fluids, as this was felt to be important for the adequate resuscitation of burn patients at that time [21]. As Moyer in the 1960s questioned the role of colloids in resuscitation regiments, he realized that patients tolerated infusions of lactated Ringers' alone at doses sufficient to keep urine output greater than 50 cm^3/h [22]. Importantly he realized that the volumes his patients were requiring for adequate resuscitation frequently exceeded calculations based on other formulas commonly used at that time.

Pruitt et al. then reviewed patients given colloid infusions in the first 24 h. He concluded, after reviewing the effects of colloid use on plasma loss rates, that colloids displayed no increased ability to restore plasma volume than equal volumes of salt solutions in the first 24 h after burn, and that colloid used in that time period represented ''merely expensive salt water'' [35]. Dr. Pruitt also carefully studied the effects of the Brooke formula on cardiac output depression seen after burn. He concluded that cardiac output returned to normal levels by 24 h after injury regardless of treatment methods. Pruitt suggested that cardiac output was a more reliable indicator of adequate resuscitation than changes in intravascular volume alone. Using these parameters, the Brooke formula was effective in preventing burn shock although Dr. Pruitt did warn that resolving cardiac output and plasma volume deficiencies did not necessarily imply that absolute

end organ perfusion was restored to normal levels. This was demonstrated using a radioactive microsphere injection technique in a burn model. Although end organ perfusion was restored to near normal in most organ systems after 4 h of resuscitation with the modified Brooke formula, a decrease in renal blood flow throughout the course of resuscitation was identified, even when cardiac parameters were normalized. This appeared minor though and was described as clinically insignificant. However, this may be inaccurate as demonstrated by a recent study from Kuwa, Jordan, and Cancio from the US Army Institute of Surgical Research in San Antonio, who used a pig model to assess renal blood flow by power Doppler imaging during burn resuscitation following a 75% TBSA scald [36]. Between hours 6 and 8 after injury, resuscitation was performed according to the Parkland formula (4 ml of lactated Ringer's solution/% burn/kg body weight/24 h), with infusion of the volume predicted for the first 8 h over hours 6–8. Between hours 8 and 10, additional volume loading was performed to achieve a pulmonary capillary wedge pressure of 16 mmHg. Then, between hours 10 and 12, dobutamine at 10 mcg/(kg min) was infused, to augment the cardiac output further. The purpose of these interventions was to permit evaluation of the accuracy of Doppler measurement of renal blood flow typical of what might be experienced during difficult burn resuscitations. Interestingly, urine output did not correlate well with renal blood flow ($r^2 = 0.25$). The resuscitation was tightly controlled with results that were not expected and reject the paradigm clinicians commonly use during resuscitation of massive burns, namely, that urine output is a surrogate for renal blood flow and therefore for cardiac output. Furthermore, the investigators showed that massive burn results in diminished cardiac output in the un-resuscitated model to levels similar to that seen by Baxter and Shires (40–50% drop) that was restored with volume loading to levels approximating those seen before injury, and further that these levels were augmented with the use of a relatively specific cardiac inotrope (dobutamine), which further increased blood flow in all measured tissues which was associated with a higher urine output.

Dr. Pruitt studied a series of patients greater than 50 years old treated at the US Army Burn Centre, and observed that an increased incidence of pulmonary edema and an increase in mortality was seen in patients that were administered resuscitation fluids at volumes that surpassed that estimated by the Brooke formula by more than 23% compared to those receiving less overall total volume. This was independent of burn size across the group. He postulated that this subgroup of patients was sensitive to fluid loading and did not support the use of formulas suggesting higher volumes of initial fluid dosing when calculating resuscitation needs [36]. Pruitt also assessed the total volumes of fluid administered to a group of adults and children, with an average 64% TBSA burn, treated at his institution with only lactated Ringer's solution in the first 24 h period after injury. He compared this to the estimated needs calculated using the Brooke formula for total volume. He found that the adult group received an average of 2.8 ml/kg/%TBSA, suggesting that the dose recommended by the Parkland formula was not supported. All fluid requirements in this group approximated what was estimated by the Brooke formula; in contrast though, children, which have a higher area to mass ratio compared to adults, required 3.75 ml/kg/%TBSA [37].

Pruitt applied these findings to what was observed regarding colloid use and proposed the modified Brooke formula, a crystalloid only (in first 24 h) resuscitation regiment, calling for colloid inclusion in the second 24 h period. This was based largely on the notion that sodium dose should be limited in severely burned patients to avoid over-resuscitation and resuscitation morbidity [35,37]. More recently, Dr. Pruitt described a phenomenon in burn resuscitation as ''fluid creep'' [38]. He states in his editorial from the Journal of Trauma, ''Adequate resuscitation has been succeeded by fluid creep, producing excessive resuscitation in the apparent belief that if some fluid is good, lots of fluid will be even better. The consequences of too much fluid can be life threatening when they take the form of the abdominal compartment syndrome …'' [38]. The consequences of increased fluid volume loading of the severely burned patient affect multiple organ systems, increasing morbidity and potentially mortality as well. The modified Brooke formula may not be effective in preventing *all* complications of fluid loading in *all* patients. The important concept is that if adequate resuscitation can be achieved beginning at a lower dose, then what can validate the use of higher dosing formulas which increase the fluid load and potential risk to the patient, especially those with minimal reserve?

5. Muir–Barclay formula

In 1974, two British surgeons, Muir and Barclay, published their experiences and recommendations regarding appropriate burn treatment. In their review of resuscitation guidelines from across the globe, they took issue with the most recent recommendations of their time as deficient in addressing the constant need for re-evaluation of the fluid resuscitation protocol in burned patients in order to prevent shock and maintain normal end organ blood flow [39]. Muir and Barclay described how Hartmann's solution (lactated Ringer's) could be sufficient for use in resuscitation protocols, yet they truly felt that reconstituted albumin represented a more physiologic, and therefore more desirable, fluid of choice. The only reason to use Hartmann's solution, in their view, was in cases where financial concerns were a factor, or albumin was unavailable. They describe the reasons for seeking a new resuscitation protocol as necessary, secondary to the disadvantages of all previous guidelines of the time where the volumes calculated are administered over ''unduly long periods'' of time in addition to complicated mathematical computations [39].

They used their knowledge of expected fluid loss rates to devise a formula, based on trials of various different schemes at Mount Vernon Hospital, which factored in multiple re-evaluations of patient response to therapy and adjustments of fluid rates. Resuscitation was based on a 36 h model broken into six time intervals (4, 10, 14, 20, 26, and 10 h). Plasma ''rations'' were calculated based on weight and % body surface burned divided by 2. Rations were adjusted as necessary, according to clinical parameters suggesting patient response, at the end of each time interval for maximal effectiveness. By

their description, volumes were rarely excessive and adjustments made in the rations were usually increases in volume, although no experimental data is presented in their text to support their claims or allow for validation of their data. The Muir/Barclay formula is still commonly used in Great Britain today. No sound evidence of benefit over today's other standards has been shown. The concern arises with this formula in that even with colloid infusions being used for the first 24 h, in stark contrast to what has been shown as ineffective by Baxter and Pruitt studies, the overall volume of fluid needs may tend be underestimated.

6. Other considerations for effective resuscitation

As is seen, absolute consensus on resuscitation formulae has not been reached. The inherent challenges faced by providers caring for severely burned casualties during the initial resuscitation period have been described previously. In November 2005, the USAISR implemented a military-wide burn resuscitation guideline that was developed along with a burn flow sheet, which required the documentation of the initial 24 h resuscitation for all severely burned casualties [40]. We found that a lower initial resuscitation volume (2 cm^3/kg/%TBSA burn vs. 4 cm^3/kg/% TBSA burn) was associated with lower total infused volume even when age, injury, and other clinical factors were accounted. However, we also did not find any difference in clinical outcomes in this small study. In a separate study, Cancio et al. described factors that help predict which patients might require increased fluid volumes to achieve adequate resuscitation over what was calculated by the modified Brooke formula [41]. He concluded that burn size and weight (negatively) were associated with greater volume requirements. In a time where decreasing the sodium load given to patients is critical, as discussed by Pruitt, it is evident by this data that the Parkland formula only leads to increased sodium loading of the patient with no increased benefit or difference in outcomes. This should be considered in prescribing volumes for initial resuscitation of the severely burned.

Abdominal compartment syndrome is of great concern to burn care providers and must be addressed in any context commenting on resuscitation volumes. ACS is associated with significant detrimental effects on multiple organ systems to include decreased pulmonary compliance, cardiac dysfunction, malperfusion to the bowel, hepatic, and renal systems. Large fluid volumes during burn resuscitation are considered a high risk for the development of ACS. Ivy et al. described their experience with intra-abdominal pressures and the relationship to fluid volumes infused in major thermal injury. They determined that an infusion approaching or surpassing 0.25 l/kg during the acute burn resuscitation greatly increases the risk of developing intra-abdominal hypertension and/or ACS [42]. Based upon this data, it is imperative that methods be delineated for decreasing overall fluid volumes dosed during initial burn resuscitations in order to prevent such a complication. This has proven to be a difficult task.

The use of colloid has been examined in decreasing overall fluid volumes and improving outcomes. In 1983, Goodwin et al. from the ISR described a randomized trial comparing the efficacy of crystalloid and colloid solutions used in burn resuscitation [43]. They concluded that the use of colloid did not provide any long lasting benefit and may even be deleterious to the pulmonary system as they showed an increase in the accumulation of lung water in those that received colloid solution, even when no inhalation injury was present. The interesting finding in the paper is that the colloid group required less fluid volume for successful resuscitation when compared to the crystalloid group. Specifically, during the 12–24 h period, clinical hemodynamic parameters were improved in the colloid group over the crystalloid group. To some, this suggests the theory that albumin leakage into the wound is over after the first 12 h. In relation to ACS, this raises the question to whether immediate use of colloid could reduce fluid volumes and subsequently ACS risk. If so, would it be at the expense of the pulmonary system? On that same note, another important question has arisen. Is plasma resuscitation better than standard colloid resuscitation in reducing fluid load and incidence intra-abdominal hypertension and ACS when compared to crystalloid in burn patients? If so, when? O'Mara et al. published their data addressing just that issue [7]. Patients were randomized to either a plasma resuscitation group or a crystalloid only group and measurements of intra-abdominal pressures were recorded and analyzed. The Parkland formula was used to calculate initial fluid requirements. They showed that the plasma group required overall less fluid loading and sustained significantly lower intra-abdominal pressures below the threshold for complications of intra-abdominal hypertension when compared to the crystalloid resuscitation arm. Although, they did also conclude that resuscitation with plasma did not improve overall outcomes as has previously been seen in colloid resuscitation studies.

One other form of resuscitation not addressed thus far regards using oral solutions for burned patients. Many of the first methods of burn resuscitation involved the use of oral solutions. In mass casualty situations or where IV fluids are not readily available, oral fluids could be easily produced at low cost. Many of these ideas stem from the treatment of severe diarrhea [44,45]. In 2003, the US Army Institute of Surgical Research collaborated with the American Burn Association in a survey of the burn bed availability in the United States should there be a national disaster [46]. The results were concerning, to say the least. It was determined that there would not be sufficient burn bed availability to handle the patient load of burns from a single mass casualty situation with over 500 severe burns. Therefore, needs for alternative resuscitation modes were deemed imperative for adequate preparedness. In 2006, investigators from San Antonio and Galveston published a historical overview of experiences with oral resuscitation therapies and gave sample recipes for homemade oral resuscitation therapies [47]. Cited were multiple investigators describing their experiences with oral resuscitation therapies throughout the 1940s–1990s using various electrolyte-based solutions. The effect of severe burn on gastrointestinal physiology, mainly ileus, poses a true roadblock to effective oral resuscitation and therefore currently supports the current standard of care, IV fluid resuscitation. A recent publication from the UTMB Galveston

Shriner's Burn Hospital group addressed the need for oral resuscitation fluid use in burns in a swine study comparing the World Health Organization Oral Resuscitation Solution, a citrate-buffered glucose electrolyte solution, to IV lactated Ringers per the Parkland formula guidelines [48]. Intestinal absorption rates were delineated and clinical parameters were compared between the groups. They concluded that enteral fluid resuscitation is feasible without detriment in a severe burn up to 40% TBSA. Any burn more severe than this could encounter maximal intestinal absorption limitations and the effectiveness of oral solutions could not be determined by their study. Lack of data to support oral solution guidelines regarding type of to be used and timing of administration after burn exist. Despite this it is concluded that oral resuscitation is feasible for use in burn shock, especially in mass casualty situations. Nonetheless, more research is imperative in order to better define the appropriateness of such guidelines.

The use of proctoclysis as a means of appropriate fluid resuscitation also has been discussed. One such protocol, the Murphy's drip, was described in 1913 by John Murphy from Chicago as an adequate means of providing appropriate fluid therapy [49]. A warmed, saline-based solution was delivered at a rate of 1.5–2 pints every 2 h. This has not caught up to the mainstream as its methods and effectiveness still require sound experimental investigation.

While choosing the appropriate resuscitation regiment to implement in a severely burned patient is difficult enough; the art of monitoring and determining if what you have prescribed is actually effective, can be just as taxing. Urine output, on an hourly basis, seems to be the most widely accepted clinical parameter to follow for evaluation of adequacy of therapy. This has relatively recently, though, been challenged [50–52]. As in earlier protocols, UOP goals were to achieve 50 cm^3/h for an average size adult. Now goals are reduced to roughly 30–35 cm^3/h for an average sized adult. Children UOP goals approximate double that of the adults, per kilogram body weight, for adequate resuscitation. Other invasive parameters have been used and challenged as well, such as central venous pressure and pulmonary artery catheters [53,54]. Invasive thermodilution monitoring is yet another form of advanced monitoring of fluid therapy with unsubstantiated results in recent trials [54]. Many other techniques have been used as well without overwhelming evidence to support their use as the standard of care. Needless to say, more studies are needed to help define better parameters for resuscitation endpoints. For example, maintaining cardiac output was the goal used in the studies leading to the Parkland formula, yet most, if any, do not use this parameter as the chief endpoint of resuscitation. Despite the fact that we have the ability to measure cardiac output, should we be focusing on it? For the meantime, then, urine output remains the standard for monitoring adequacy of resuscitation after severe burn unless a fruitful alternative comes to bear.

One more very important question regarding resuscitation has arisen regarding the immunomodulatory effects of lactated Ringers'. Some suggest that use of this particular fluid may be of actual harm. Rhee et al. presented such a case at the 1997 Annual Meeting of the Western Trauma Association [55]. There, they discussed the results of a study in swine which they concluded that LR was responsible for increased neutrophil activation after resuscitation for hemorrhage or after infusion without hemorrhage. LR used in the majority of hospitals contains a racemic mixture of the D-lactate and L-lactate isomers. L-Lactate is the more natural form normally found in mammalian metabolism. A more recent study of the separate effects of each isomer on human leukocytes revealed that the D-lactate isomer was actually responsible for an observed increased production of reactive oxygen species and effects on gene expression leading to increased apoptosis seen after exposure to the racemic formulation of LR [56]. Neurocardiac toxicity with serious consequences has also been described in animal models by infusion of D-lactate LR compared to no toxic signs seen when given only L-lactate LR [57]. Some manufactures are now producing LR containing only the L-lactate isomer. As long as crystalloid and therefore LR remains the standard of care for initial fluid resuscitation, the growing body of evidence regarding using racemic formulations of LR is seriously called into question and should have no role in any resuscitation.

7. Current effectiveness of accepted guidelines

In most places, two formulas are accepted as guidelines for the resuscitation of severely burned patients, the Parkland and modified Brooke formulas. Burn care providers of all specialties are trained in the use of these formulas in order to help prevent the onset of burn shock prior to the patient's arrival in a burn centre with experienced burn staff. Unfortunately, in the ''heat of the moment'', inexperienced first responders as well as many higher level emergency care physicians fail to have recall of the appropriate calculations for adequate fluid needs of the patient. Burn size, which is used for fluid volume calculations, is commonly grossly under- or overestimated by inexperienced providers [58]. This is possibly due to anxiety induced by the situation in concert with the multiple formulas with multiple variables to remember, making it difficult to correctly implement. This leads to a high rate of non-compliance seen in following these resuscitation guidelines often leading to over- or under-resuscitation. In 2004, Bhat et al. published the results of a two-phase survey study in which they polled physicians and students on their recall and use of resuscitation formulas [59]. One-hundred and ninety-eight Emergency Medicine physicians in the US and United Kingdom were asked for their knowledge on accurately recalling any resuscitation formula and specifics relating to any correct formula recalled. The second phase of the study tested the ability of 22 medical students, given the correct formula and case studies, to correctly compute the appropriate fluid therapy for the patients described in each case study. Results of the first phase showed that 4% of those in the United Kingdom and 33% of those in the US could accurately recall a standard resuscitation formula. In the students, even after being supplied with the correct formulas, large miscalculations occurred. This can be deadly for patients, especially those with deficient reserve. The authors of the study argue that a simplified initial resuscitation protocol is necessary. At the USAISR we are currently implementing just that, a simplified resuscitation formula named 'The Rule of

Ten' (ROT), which falls within ABA acceptable guidelines for fluid therapy [60]. 'The Rule of Ten', which consists of two steps, eliminates the confusion of recalling a difficult formula and its accurate implementation. First, the estimated burn size in %TBSA is multiplied by 10 to derive the initial fluid rate in ml/h. For every 10 kg above 80 kg, 100 ml is added to this rate. When compared directly to the Parkland and modified Brooke formulas, the fluid rate would be overestimated for patients under 40 kg, while underestimated for patients over 140 kg. The 'Rule of Ten' is currently implemented as protocol at our institution and can easily be used to rapidly estimate the initial fluid rate for the majority of adult patients. Simple and rapid calculation of the initial fluid rate will allow pre-hospital and other emergency care providers to focus their attention on the process of resuscitation. Further adjustments to fluid rate can be made based on clinical observations of effect.

8. Future considerations

The reality of burn resuscitation evolution is that our guidelines have been in place for 40 years with no significant changes despite the findings of continued complications during resuscitation [9]. Complications remain possibly as result of overzealous over-resuscitation, irresponsible under-resuscitation, or simply the lack of recall for complex formulas. The formula developed in the 1960s and 1970s was designed for the technology and monitoring of the time. Urine output was generally not measured hourly, nor was the monitoring of vital signs made continuously as it is today. The formulas were devised as guidelines for 24 and 48 h of treatment with no designed provision for routine close monitoring of the response to treatment. Perhaps this is best exemplified by the recommendation of the Parkland formula to decrease fluid volume administration at 8 h after injury regardless of patient condition. Nowadays, our severely burned patients are adorned with electrocardiography leads, Foley catheters, arterial and central venous lines, near-infrared spectrophotometers, oxygen saturation monitors, and end-tidal carbon dioxide monitors, among others, that give us almost continuous feedback of physiologic events occurring in the patient. The mere presence of these monitors engenders the need to make adjustments of treatment on a similarly continuous basis. Venkatesh et al. described the use of tissue perfusion monitoring devices to demonstrate that in light of acceptable clinical indices of global perfusion seen during the resuscitation of severely burned patients, tissue perfusion of burnt and normal skin as well as the splanchnic circulation can remain compromised [61]. Therefore, it seems that in response to the more rapid feedback that perhaps a better approach would be to devise an appropriate starting infusion dose, and adjust accordingly based on feedback from the individual patient rather than rely on data derived from populations of patients. This notion, however, implies that the

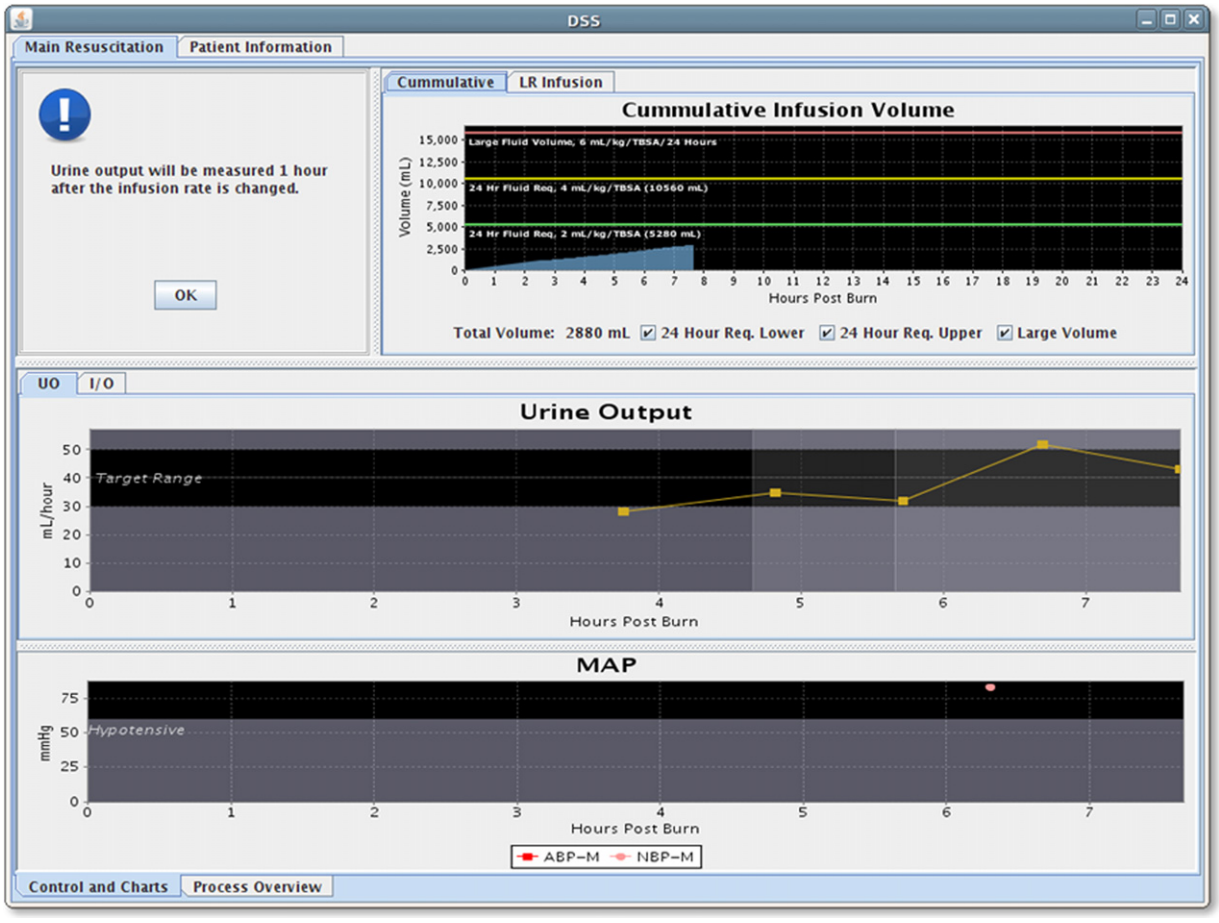

Fig. 3 – Computer interface of resuscitation decision support system from USAISR.

feedback received from our monitors actually reflects physiologic condition. With this assumption in mind, then perhaps automated decision support systems that take physiologic feedback into account and make recommendations for changes in treatment in a timely fashion would be more appropriate [62]. At the United States Army Institute of Surgical Research in collaboration with investigators in Galveston, we have embarked on such a program with initial fluid administration rates determined by the 'Rule of Ten' [60]. From this point, adjustments are made hourly based on measured urine output entered into a decision support algorithm derived from close monitoring of 40 severely burned patients (Fig. 3). We are closely monitoring the adequacy of resuscitating patients in this fashion, and will subsequently assess the role of colloid in resuscitation, specifically the utility of plasma.

Another key consideration now coming to the forefront of therapy is that of high volume hemofiltration for those patients that develop shock or have difficult resuscitations [63–65]. The current belief is that capillary leakage that leads to fluid losses and needs for large amounts of fluid therapy are mediated by pro- and anti-inflammatory mediators. The exact mechanism of how these mediators act in concert to produce such profound capillary integrity disruption is not known. The use of hemofiltration devices to remove such mediators has shown encouraging results. The USAISR has presented data on the use of high volume hemofiltration in burn patients developing septic shock and has shown and decreased in hospital mortality in the study [66]. More patients across multiple centres are needed to verify these findings and their application to burn shock as well. The exact pathophysiology of severe burn and the mediators involved need to be elucidated before any great advances can potentially be made. Hemofiltration devices may just help unearth the mystery.

9. Summation

The resuscitation of severely burned patients has clearly evolved over the last century, with a lull in significant progress since the 1970s, at the expense of the patient in our opinion. The guidelines used today were developed 40 years ago, yet remain the mainstay of current initial fluid therapy despite ongoing research. Preventing complications of over- or under-resuscitation still confounds burn providers as no recent advances have been made in this arena as well. As we continue to investigate new ways to address current fluid therapy needs, monitor end points of resuscitation, and prevent the negative effects of our current therapies; it is of absolute importance that we head in the new century with a strong focus on elucidating the mysteries of burn pathophysiology. It is at that time only that we can provide targeted fluid resuscitation therapy that will change the way we practice from today's standard of care to the benefit of our patients.

Conflict of interest

None.

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